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A Comparison of FDA and EMA Pregnancy and Lactation Labeling

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Disclaimer

I do not have any financial disclosures to report.

This presentation represents the views of the speaker, and not the official position of the FDA.

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Introduction

- The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have robust collaboration and dialogue around the need for data and the inclusion of pregnant and lactating individuals in clinical research.
- Despite this collaboration, the two agencies have their own standards for the format and content of labeling for these populations.

Objectives

1. Compare the EMA and the FDA labeling on new drug marketing applications for drugs that might be prescribed for females of reproductive potential

2. Determine whether there are consistent similarities or differences

3. Ascertain where there might be opportunities to learn from each other's approaches

Methods: Data Source

Comparative Study > Clin Pharmacol Ther. 2020 Jan;107(1):195-202. doi: 10.1002/cpt.1565. Epub 2019 Aug 14.

A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why

Mwango Kashoki [1,2], Zahra Hanaizi [3], Stella Yordanova [3], Richard Veselý [3], Christelle Bouygues [3], Jordi Llinares [3], Sandra L Kweder [4]

- We compared approved labeling, specifically pregnancy and lactation sections, in order to gain insights to these questions.
- In total, this cohort included 98 new chemical or biological entity marketing applications approved on the first cycle of review by EMA and FDA and served as the source of the sample for this study.

Methods: Inclusion/Exclusion Criteria

- Exclusion Criteria: drugs approved only for men and postmenopausal women,
- We chose a sample of 35 drugs that could be used by females of reproductive potential
- Four drugs for which the manufacturer withdrew the marketing application after approval were also excluded, which resulted in the final cohort of 31 approved drugs.

Methods: FDA Labeling

FDA Labeling/Package Insert

8.1 Pregnancy	8.2 Lactation	8.3 Females and Males of Reproductive Potential
• Pregnancy Registry • Risk Summary • Clinical Considerations • Data	• Risk Summary • Clinical Considerations • Data	• Pregnancy Testing • Contraception • Infertility

Methods: EMA Labeling

EMA Summary of Product Characteristics (SmPC)

Women of Childbearing Potential	Pregnancy	Lactation	Fertility
• Recommendation for use • Pregnancy Testing • Contraception	• Available data • Recommendation for use • Example statements for use during pregnancy	• Available data • Recommendation for use • Example statements for use during breastfeeding	• Available data

Methods: Defining Inclusion of Human Data in Pregnancy Labeling

The EMA Definition for Inclusion of Human Data in Pregnancy*:

- No or limited amount of data from the use of [generic drug name] in pregnant women
  - Less than 300 exposure outcomes
- Moderate Amount of Human Data
  - Between 300 and 1,000 exposure outcomes
- Large Amount of Human Data
  - Greater than 1,000 exposure outcomes

The FDA has no such definition for inclusion of human data in pregnancy labeling.

Study Definition for Inclusion of Human Data in Pregnancy Labeling:

- No or a limited amount of human data
- Human Data (≥300 exposure outcomes)

*EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling Appendix 3

Methods: Defining Inclusion of Human Data in Lactation Labeling

The EMA and the FDA have no definition for inclusion of human data for lactation labeling.

Study Definition for Inclusion of Human Data in Lactation Labeling:

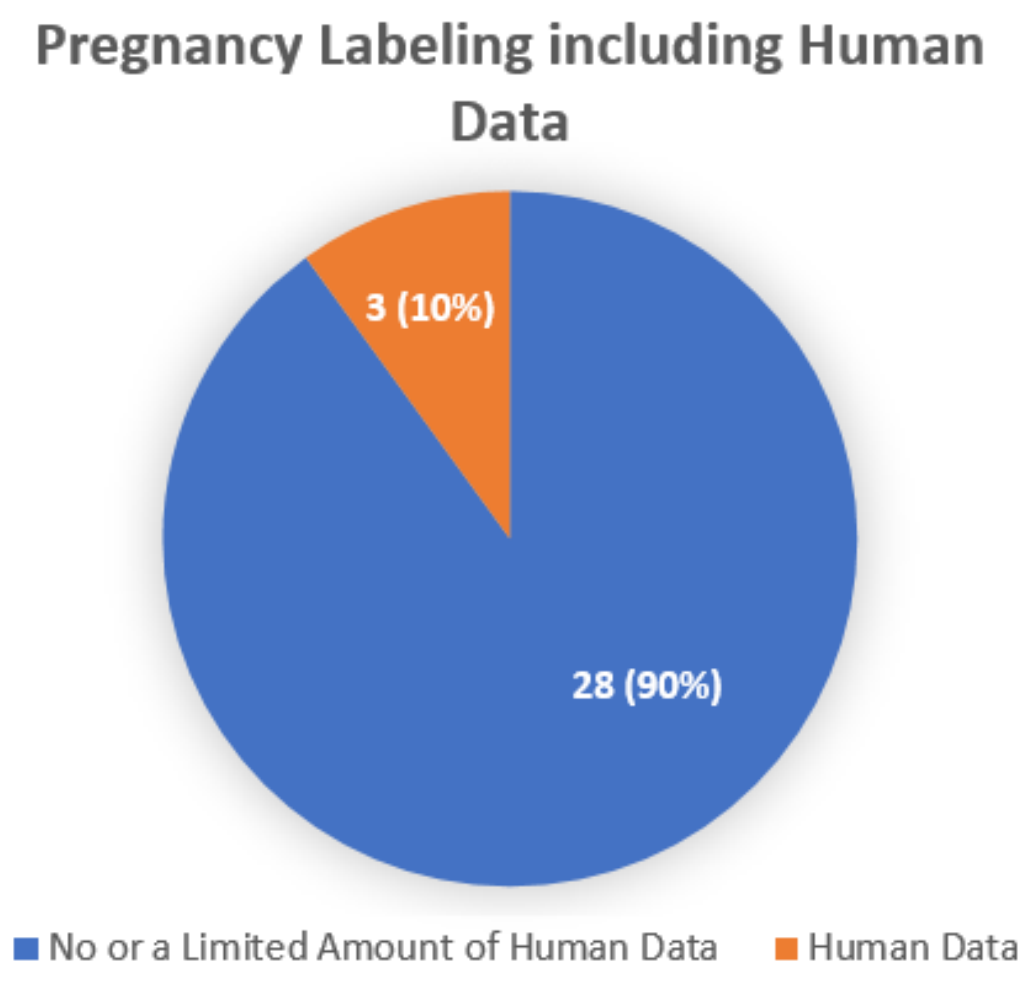
- No Human data
- Human Data

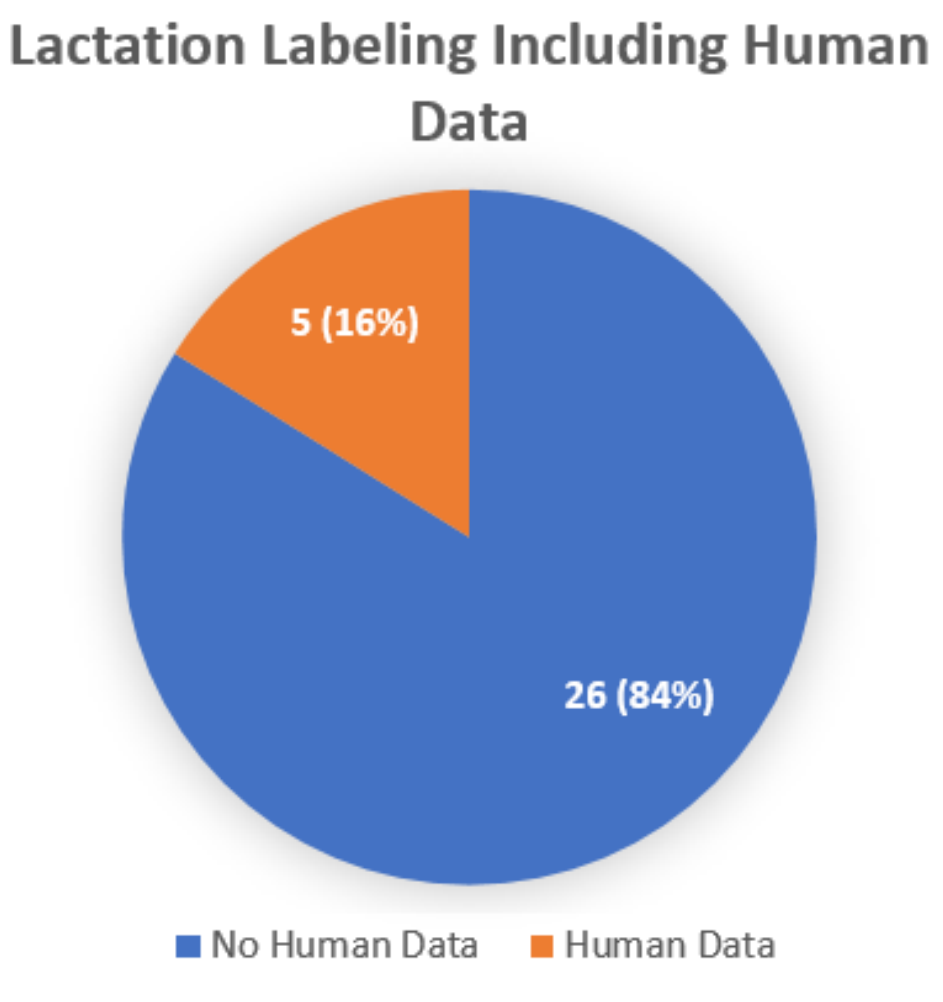
Methods: Comparing Labeling Language

Language that does not Discourage Use
Stated:
○ can be used or may be considered ○ benefit-risk consideration ○ data without a recommendation

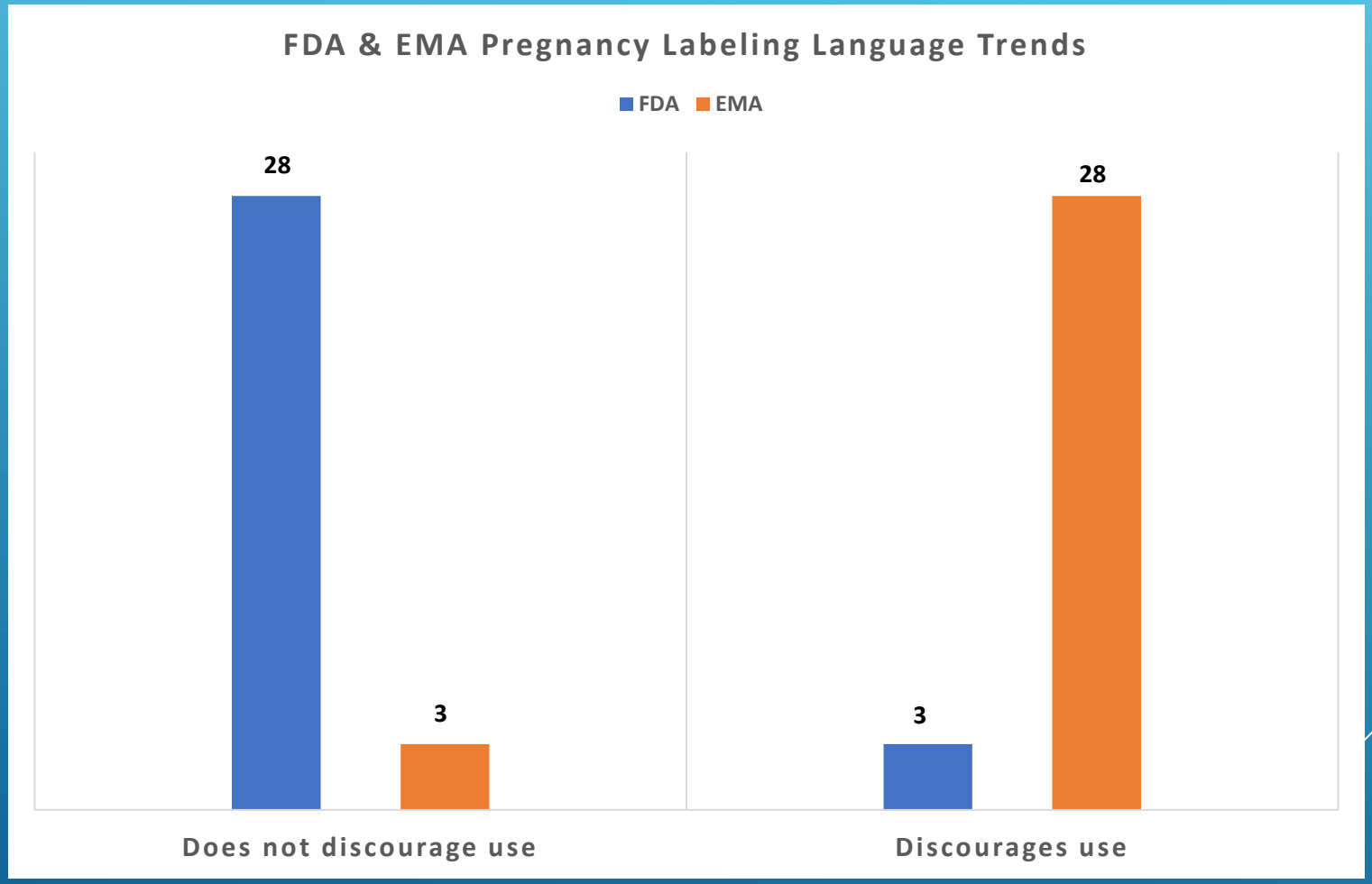
Language that Discourages Use
Stated:
○ avoid use ○ should not be administered, should not be used, or should be discontinued ○ contraindicated, or not recommended during pregnancy and while breastfeeding

Results: Assessment of Presence of Human Data in Pregnancy and Lactation Labeling

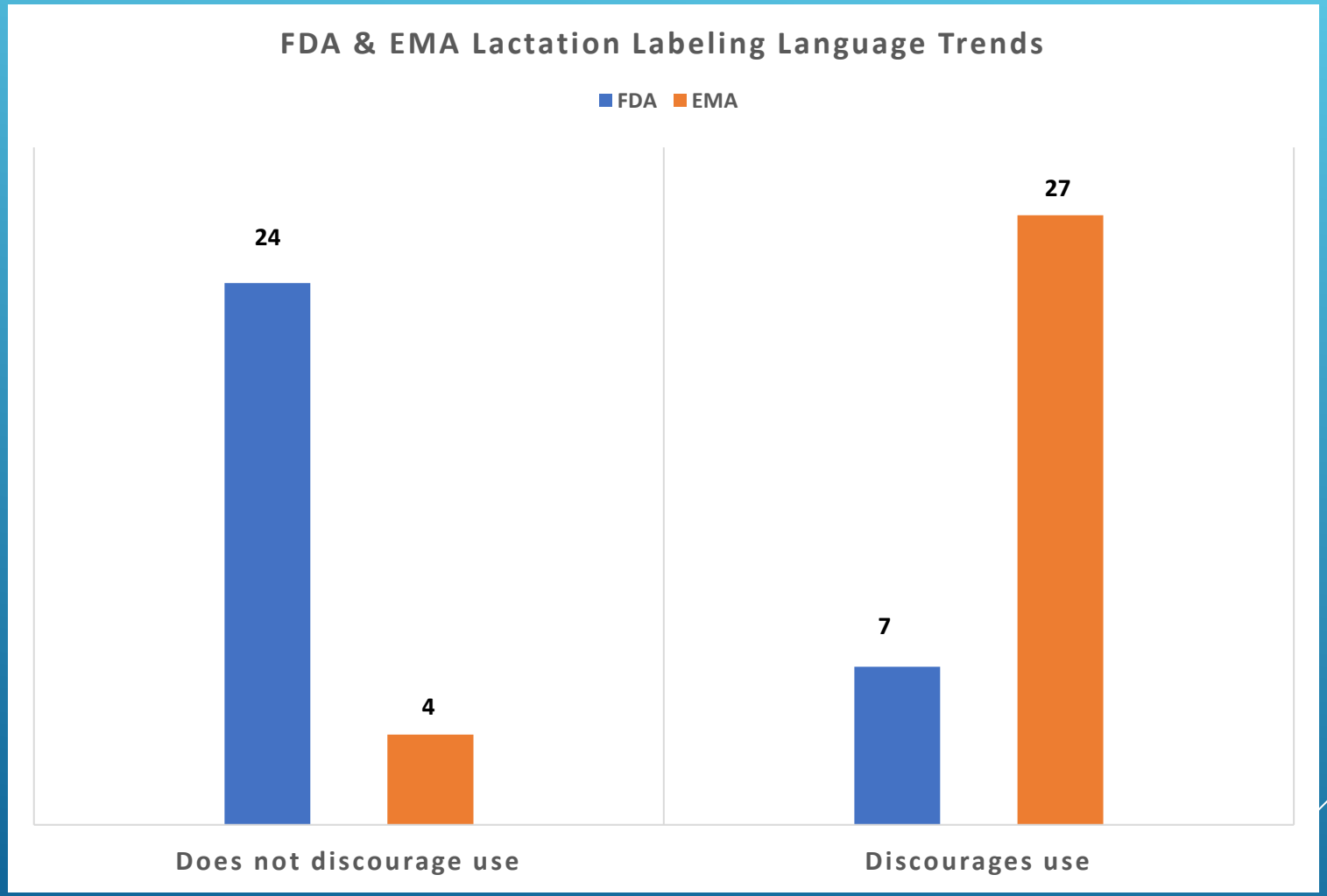




Results: Comparison of FDA and EMA Pregnancy Labeling Language Trends



Results: Comparison of FDA and EMA Lactation Labeling Language Trends



Results: Pregnancy Language Concordance and Discordance between the FDA and the EMA

FDA and EMA Pregnancy Labeling Language Concordance

Human Data Available	Concordant Language (n= 10)*	Discordant Language (n=21)
Yes	3	0
No or a limited amount	7*	21

Discordant pregnancy labeling: Language differences between the EMA and FDA

FDA Labeling	EMA Labeling	Number of products
No specific recommendation, only data presentation	Recommendations ranging from avoiding use to contraindicating use in pregnancy	13
Advise of a potential (not quantified) risk		3
Recommends consideration of benefit/risk in deciding use		4
Specific mention of benefit and risk consideration during labor	Specific mention of benefit and risk consideration during pregnancy	1

Results: Lactation Standard Statements

FDA Standard Statement: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (drug) and any potential adverse effects on the breastfed infant from (drug) or from the underlying maternal condition.

EMA Standard Statement: Because of the potential for adverse reactions in breastfed infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from (drug) therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Results: Lactation Language Concordance and Discordance between the FDA and the EMA

FDA and EMA Lactation Labeling Language Concordance

Human Data Available	Concordant Language (n= 9)*	Discordant Language (n=22)
Yes	3	2
No	6*	20

Discordant Lactation labeling: Language differences between EMA and FDA

FDA Labeling	EMA Labeling	Number of products
Standard Statement*	Standard Statement **	15
	Should not be used/discontinue use	5
	Can be used	1
Not recommended	Standard Statement	1

Discussion: Language Concordance and Discordance

- The EMA's language in the pregnancy and lactation sections of labeling was more directive, while the FDA language simply stated the data or allowed the prescriber to make a benefit-risk assessment
- Concordance in labeling language for pregnancy and lactation is not the norm.

Discussion: Language Concordance and Discordance

- A drug approved for plaque psoriasis provides a good example of these differences.
  - The EMA labeling contraindicates use during pregnancy.
  - The FDA labeling states that available pharmacovigilance data have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes and advises of risk of fetal loss based on animal data.

Discussion: Need for Human Data to Inform Prescribing Decisions

- Lack of human data relevant to pregnant and lactating populations has long been highlighted as an area of significant public health need.
- Only 10% of pregnancy labeling and 16% of lactation labeling including human data, although pregnant and lactating individuals are likely to have been prescribed them since their approval.

Conclusion

- There is a need for global collaboration, communication, and alignment
- New opportunities:
  - Pregnancy and Lactation Cluster
  - New ICH guideline development on the Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials

Acknowledgments

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